

WHAT IS CLAIMED IS:

1. A vitamin receptor binding drug delivery conjugate comprising:
- 5 (a) a vitamin receptor binding moiety;
- (b) a bivalent linker; and
- (c) a drug, or an analog or derivative thereof;
- wherein the vitamin receptor binding moiety is covalently linked to the bivalent linker;
- the drug, or the analog or the derivative thereof, is covalently linked to
- 10 the bivalent linker; and
- the bivalent linker comprises one or more components selected from the group consisting of spacer linkers, releasable linkers, and heteroatom linkers, and combinations thereof;
- providing that the bivalent linker includes at least one releasable linker
- 15 that is not a disulfide.
2. The drug delivery conjugate of claim 1 wherein the vitamin receptor binding moiety is selected from the group consisting of vitamins, and vitamin receptor binding analogs and derivatives thereof.
3. The drug delivery conjugate of claim 1 wherein the heteroatom
- 20 linker is a nitrogen, oxygen, or sulfur atom, or is selected from the group of formulae consisting of $\text{-NHR}^1\text{NHR}^2\text{-}$, -SO- , $\text{-S(O)}_2\text{-}$, and $\text{-NR}^3\text{O-}$, wherein R^1 , R^2 , and R^3 are each independently selected from the group consisting of hydrogen, alkyl, aryl, arylalkyl, substituted aryl, substituted arylalkyl, heteroaryl, substituted heteroaryl, and alkoxyalkyl.
- 25 4. The drug delivery conjugate of claim 1 wherein the spacer linker is selected from the group consisting of carbonyl, thionocarbonyl, alkylene, cycloalkylene, alkylencycloalkyl, alkylenecarbonyl, cycloalkylenecarbonyl, carbonylalkylcarbonyl, 1-alkylenesuccinimid-3-yl, 1-(carbonylalkyl)succinimid-3-yl, alkylenesulfoxyl, sulfonylalkyl, alkylenesulfoxylalkyl, alkylenesulfonylalkyl,
- 30 carbonyltetrahydro-2H-pyranyl, carbonyltetrahydrofuranyl, 1-(carbonyltetrahydro-2H-pyranyl)succinimid-3-yl, and 1-(carbonyltetrahydrofuranyl)succinimid-3-yl,

wherein each of said spacer linkers is optionally substituted with one or more substituents X^1 ;

wherein each substituent X^1 is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, hydroxy, hydroxyalkyl, amino, aminoalkyl, 5 alkylaminoalkyl, dialkylaminoalkyl, halo, haloalkyl, sulfhydrylalkyl, alkylthioalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, carboxy, carboxyalkyl, alkyl carboxylate, alkyl alkanoate, guanidinoalkyl, R^4 -carbonyl, R^5 -carbonylalkyl, R^6 -acylamino, and R^7 -acylaminoalkyl, wherein R^4 and R^5 are each independently selected from the group consisting of an amino acid, an 10 amino acid derivative, and a peptide, and wherein R^6 and R^7 are each independently selected from the group consisting of an amino acid, an amino acid derivative, and a peptide.

5. The drug delivery conjugate of claim 4 wherein the heteroatom linker is nitrogen, and wherein the substituent X^1 and the heteroatom linker are taken 15 together with the spacer linker to which they are bound to form an heterocycle.

6. The drug delivery conjugate of claim 5 wherein the heterocycle is selected from the group consisting of pyrrolidines, piperidines, oxazolidines, isoxazolidines, thiazolidines, isothiazolidines, pyrrolidinones, piperidinones, oxazolidinones, isoxazolidinones, thiazolidinones, isothiazolidinones, and 20 succinimides.

7. The drug delivery conjugate of claim 1 wherein the releasable linker is selected from the group consisting of methylene, 1-alkoxyalkylene, 1-alkoxycycloalkylene, 1-alkoxyalkylenecarbonyl, 1-alkoxycycloalkylenecarbonyl, carbonylarylcabonyl, carbonyl(carboxyaryl)carbonyl, 25 carbonyl(biscarboxyaryl)carbonyl, haloalkylenecarbonyl, alkylene(dialkylsilyl), alkylene(alkylarylsilyl), alkylene(diarylsilyl), (dialkylsilyl)aryl, (alkylarylsilyl)aryl, (diarylsilyl)aryl, oxycarbonyloxy, oxycarbonyloxyalkyl, sulfonylalkyl, iminoalkylidenyl, carbonylalkylideniminyl, iminocycloalkylidenyl, carbonylcycloalkylideniminyl, alkylenesulfonyl, alkyleneethio, alkylenearylthio, and 30 carbonylalkylthio, wherein each of said releasable linkers is optionally substituted with one or more substituents X^2 ;

wherein each substituent X^2 is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, hydroxy, hydroxyalkyl, amino, aminoalkyl,

alkylaminoalkyl, dialkylaminoalkyl, halo, haloalkyl, sulfhydrylalkyl, alkylthioalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, carboxy, carboxyalkyl, alkyl carboxylate, alkyl alkanoate, guanidinoalkyl, R⁴-carbonyl, R⁵-carbonylalkyl, R⁶-acylamino, and R⁷-acylaminoalkyl, wherein R⁴ and R⁵ are each independently selected from the group consisting of an amino acid, an amino acid derivative, and a peptide, and wherein R⁶ and R⁷ are each independently selected from the group consisting of an amino acid, an amino acid derivative, and a peptide.

8. The drug delivery conjugate of claim 7 wherein the heteroatom linker is nitrogen, and wherein the substituent X² and the heteroatom linker are taken together with the releasable linker to which they are bound to form an heterocycle.

9. The drug delivery conjugate of claim 8 wherein the heterocycle is selected from the group consisting of pyrrolidines, piperidines, oxazolidines, isoxazolidines, thiazolidines, isothiazolidines, pyrrolidinones, piperidinones, oxazolidinones, isoxazolidinones, thiazolidinones, isothiazolidinones, and succinimides.

10. The drug delivery conjugate of claim 1 wherein the heteroatom linker is nitrogen, and wherein the releasable linker and the heteroatom linker are taken together to form a divalent radical comprising alkyleneaziridin-1-yl, alkylencarbonylaziridin-1-yl, carbonylalkylaziridin-1-yl, alkylenesulfoxylaziridin-1-yl, sulfoxylalkylaziridin-1-yl, sulfonylalkylaziridin-1-yl, or alkylenesulfonylaziridin-1-yl, wherein each of said releasable linkers is optionally substituted with one or more substituents X²;

wherein each substituent X² is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, hydroxy, hydroxyalkyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, halo, haloalkyl, sulfhydrylalkyl, alkylthioalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, carboxy, carboxyalkyl, alkyl carboxylate, alkyl alkanoate, guanidinoalkyl, R⁴-carbonyl, R⁵-carbonylalkyl, R⁶-acylamino, and R⁷-acylaminoalkyl, wherein R⁴ and R⁵ are each independently selected from the group consisting of an amino acid, an amino acid derivative, and a peptide, and wherein R⁶ and R⁷ are each independently selected from the group consisting of an amino acid, an amino acid derivative, and a peptide.

11. The drug delivery conjugate of claim 10 wherein the heteroatom linker is nitrogen, and the releasable linker and the heteroatom linker are taken together to form a divalent radical comprising alkyleneaziridin-1-yl, carbonylalkylaziridin-1-yl, sulfoxylalkylaziridin-1-yl, or sulfonylalkylaziridin-1-yl.

12. The drug delivery conjugate of claim 11 wherein the spacer linker is selected from the group consisting of carbonyl, thionocarbonyl, alkylencarbonyl, cycloalkylencarbonyl, carbonylalkylcarbonyl, and 1-(carbonylalkyl)succinimid-3-yl, wherein each of said spacer linkers is optionally substituted with one or more substituents X^1 ;

wherein each substituent X^1 is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, hydroxy, hydroxyalkyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, halo, haloalkyl, sulfhydrylalkyl, alkylthioalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, carboxy, carboxyalkyl, alkyl carboxylate, alkyl alkanoate, guanidinoalkyl, R^4 -carbonyl, R^5 -carbonylalkyl, R^6 -acylamino, and R^7 -acylaminoalkyl, wherein R^4 and R^5 are each independently selected from the group consisting of an amino acid, an amino acid derivative, and a peptide, and wherein R^6 and R^7 are each independently selected from the group consisting of an amino acid, an amino acid derivative, and a peptide;

and wherein the spacer linker is bonded to the releasable linker to form an aziridine amide.

13. The drug delivery conjugate of claim 1 wherein the drug is a mitomycin, a mitomycin derivative, or a mitomycin analog, and the releasable linker is selected from the group consisting of carbonylalkylthio, carbonyltetrahydro-2H-pyranyl, carbonyltetrahydrofuran-1-yl, 1-(carbonyltetrahydro-2H-pyranyl)succinimid-3-yl, and 1-(carbonyltetrahydrofuran-1-yl)succinimid-3-yl, wherein each of said releasable linkers is optionally substituted with one or more substituents X^2 ,

wherein each substituent X^2 is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, hydroxy, hydroxyalkyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, halo, haloalkyl, sulfhydrylalkyl, alkylthioalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, carboxy, carboxyalkyl, alkyl carboxylate, alkyl alkanoate, guanidinoalkyl, R^4 -carbonyl, R^5 -carbonylalkyl, R^6 -acylamino, and R^7 -acylaminoalkyl, wherein R^4 and

R⁵ are each independently selected from the group consisting of an amino acid, an amino acid derivative, and a peptide, and wherein R⁶ and R⁷ are each independently selected from the group consisting of an amino acid, an amino acid derivative, and a peptide;

5 and wherein the aziridine of the mitomycin is bonded to the releasable linker to form an acylaziridine.

14. The drug delivery conjugate of claim 1 wherein the drug includes a double-bonded nitrogen atom, wherein the releasable linker is selected from the group consisting of alkylencarbonylamino and
10 1-(alkylencarbonylamino)succinimid-3-yl, and wherein the releasable linker is bonded to the drug nitrogen to form an hydrazone.

15. The drug delivery conjugate of claim 1 wherein the drug includes a sulfur atom, the releasable linker is selected from the group consisting of alkylenthio and carbonylalkylthio, and wherein the releasable linker is bonded to the
15 drug sulfur to form a disulfide.

16. The drug delivery conjugate of claim 4 wherein the vitamin receptor binding moiety is folate which includes a nitrogen, and the spacer linker is selected from the group consisting of alkylencarbonyl, cycloalkylencarbonyl, carbonylalkylcarbonyl, and 1-(carbonylalkyl)succinimid-3-yl, wherein the spacer
20 linker is bonded to the folate nitrogen to form an imide or an alkylamide.

17. The drug delivery conjugate of claim 16 wherein each substituent X¹ is independently selected from the group consisting of alkyl, hydroxyalkyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfhydrylalkyl, alkylthioalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, carboxy, carboxyalkyl, guanidinoalkyl, R⁴-carbonyl, R⁵-carbonylalkyl, R⁶-acylamino, and R⁷-acylaminoalkyl, wherein R⁴ and R⁵ are each independently selected from the group consisting of an amino acid, an amino acid derivative, and a peptide, and wherein R⁶ and R⁷ are each independently selected from the group consisting of an amino acid, an amino acid derivative, and a peptide.

18. The drug delivery conjugate of claim 4 wherein the heteroatom linker is nitrogen, and the spacer linker is selected from the group consisting of alkylencarbonyl, cycloalkylencarbonyl, carbonylalkylcarbonyl, and 1-(carbonylalkyl)succinimid-3-yl, wherein each of said spacer linkers is optionally

substituted with one or more substituents X^1 and the spacer linker is bonded to the nitrogen to form an amide.

19. The drug delivery conjugate of claim 4 wherein the heteroatom linker is sulfur, and the spacer linker is selected from the group consisting of alkylene and cycloalkylene, wherein each of said spacer linkers is optionally substituted with
5 carboxy, and the spacer linker is bonded to the sulfur to form a thiol.

20. The drug delivery conjugate of claim 4 wherein the heteroatom linker is sulfur, and the spacer linker is selected from the group consisting of 1-alkylenesuccinimid-3-yl and 1-(carbonylalkyl)succinimid-3-yl, and the spacer
10 linker is bonded to the sulfur to form a succinimid-3-ylthiol.

21. The drug delivery conjugate of claim 7 wherein the heteroatom linker is oxygen, and the releasable linker is selected from the group consisting of methylene, 1-alkoxyalkylene, 1-alkoxycycloalkylene, 1-alkoxyalkylenecarbonyl, and 1-alkoxycycloalkylenecarbonyl, wherein each of said releasable linkers is optionally
15 substituted with one or more substituents X^2 , and the releasable linker is bonded to the oxygen to form an acetal or ketal.

22. The drug delivery conjugate of claim 7 wherein the heteroatom linker is oxygen, and the releasable linker is methylene, wherein said methylene is substituted with an optionally-substituted aryl, and the releasable linker is bonded to
20 the oxygen to form an acetal or ketal.

23. The drug delivery conjugate of claim 7 wherein the drug includes a nitrogen atom, the heteroatom linker is nitrogen, and the releasable linker is selected from the group consisting of carbonylarylcarbonyl, carbonyl(carboxyaryl)carbonyl, carbonyl(biscarboxyaryl)carbonyl, and the releasable
25 linker is bonded to the heteroatom linker nitrogen to form an amide, and also bonded to the drug nitrogen to form an amide.

24. The drug delivery conjugate of claim 7 wherein the drug includes an oxygen atom, the heteroatom linker is nitrogen, and the releasable linker is selected from the group consisting of carbonylarylcarbonyl, carbonyl(carboxyaryl)carbonyl, carbonyl(biscarboxyaryl)carbonyl, and the releasable
30 linker is bonded to the heteroatom linker nitrogen to form an amide, and also bonded to the drug oxygen to form an ester.

25. The drug delivery conjugate of claim 7 wherein the heteroatom linker is nitrogen, and the releasable linker is selected from the group consisting of iminoalkylidenyl, carbonylalkylideniminyl, iminocycloalkylidenyl, and carbonylcycloalkylideniminyl, wherein each of said releasable linkers is optionally substituted with one or more substituents X^2 , and the releasable linker is bonded to the nitrogen to form an hydrazone.

26. The drug delivery conjugate of claim 7 wherein the heteroatom linker is oxygen, and the releasable linker is selected from the group consisting of alkylene(dialkylsilyl), alkylene(alkylarylsilyl), alkylene(diarylsilyl), (dialkylsilyl)aryl, (alkylarylsilyl)aryl, and (diarylsilyl)aryl, wherein each of said releasable linkers is optionally substituted with one or more substituents X^2 , and the releasable linker is bonded to the oxygen to form a silanol.

27. The drug delivery conjugate of claim 1 wherein the drug includes a nitrogen atom, and the releasable linker is haloalkylenecarbonyl, optionally substituted with one or more substituents X^2 ;

wherein each substituent X^2 is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, hydroxy, hydroxyalkyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, halo, haloalkyl, sulfhydrylalkyl, alkylthioalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, carboxy, carboxyalkyl, alkyl carboxylate, alkyl alkanoate, guanidinoalkyl, R^4 -carbonyl, R^5 -carbonylalkyl, R^6 -acylamino, and R^7 -acylaminoalkyl, wherein R^4 and R^5 are each independently selected from the group consisting of an amino acid, an amino acid derivative, and a peptide, and wherein R^6 and R^7 are each independently selected from the group consisting of an amino acid, an amino acid derivative, and a peptide;

and the releasable linker is bonded to the drug nitrogen to form an amide.

28. The drug delivery conjugate of claim 1 wherein the drug includes an oxygen atom, and the releasable linker is alkyleneoxycarbonyl or haloalkylenecarbonyl, optionally substituted with one or more substituents X^2 ;

wherein each substituent X^2 is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, hydroxy, hydroxyalkyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, halo, haloalkyl, sulfhydrylalkyl, alkylthioalkyl,

aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, carboxy, carboxyalkyl, alkyl carboxylate, alkyl alkanoate, guanidinoalkyl, R⁴-carbonyl, R⁵-carbonylalkyl, R⁶-acylamino, and R⁷-acylaminoalkyl, wherein R⁴ and R⁵ are each independently selected from the group consisting of an amino acid, an amino acid derivative, and a peptide, and wherein R⁶ and R⁷ are each independently selected from the group consisting of an amino acid, an amino acid derivative, and a peptide;

and the releasable linker is bonded to the drug oxygen to form a carbonate or an ester.

10 29. The drug delivery conjugate of claim 1 wherein the heteroatom linker is oxygen, the spacer linker is 1-alkylenesuccinimid-3-yl, optionally substituted with one or more substituents X¹, and the releasable linker is selected from the group consisting of methylene, 1-alkoxyalkylene, 1-alkoxycycloalkylene, 1-alkoxyalkylenecarbonyl, 1-alkoxycycloalkylenecarbonyl, wherein each of said
15 releasable linkers is optionally substituted with one or more substituents X²;

 wherein each substituent X² is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, hydroxy, hydroxyalkyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, halo, haloalkyl, sulfhydrylalkyl, alkylthioalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted
20 heteroaryl, carboxy, carboxyalkyl, alkyl carboxylate, alkyl alkanoate, guanidinoalkyl, R⁴-carbonyl, R⁵-carbonylalkyl, R⁶-acylamino, and R⁷-acylaminoalkyl, wherein R⁴ and R⁵ are each independently selected from the group consisting of an amino acid, an amino acid derivative, and a peptide, and wherein R⁶ and R⁷ are each independently selected from the group consisting of an amino acid, an amino acid derivative, and a
25 peptide;

and wherein the spacer linker and the releasable linker are each bonded to the heteroatom linker to form a succinimid-1-ylalkyl acetal or ketal.

 30. The drug delivery conjugate of claim 1 wherein the bivalent linker comprises an heteroatom linker, a spacer linker, and a releasable linker taken
30 together to form 3-thiosuccinimid-1-ylalkyloxymethyloxy, where the methyl is optionally substituted with alkyl or substituted aryl.

 31. The drug delivery conjugate of claim 1 wherein the bivalent linker comprises an heteroatom linker, a spacer linker, and a releasable linker taken

together to form 3-thiosuccinimid-1-ylalkylcarbonyl, where the carbonyl forms an acylaziridine with the drug, or analog or derivative thereof.

32. The drug delivery conjugate of claim 1 wherein the bivalent linker comprises an heteroatom linker, a spacer linker, and a releasable linker taken
5 together to form 1-alkoxycycloalkylenoxy.

33. The drug delivery conjugate of claim 1 wherein the bivalent linker comprises a spacer linker, an heteroatom linker, and a releasable linker taken together to form alkyleneaminocarbonyl(dicarboxylarylene)carboxylate.

34. The drug delivery conjugate of claim 1 wherein the bivalent
10 linker comprises a releasable linker, a spacer linker, and a releasable linker taken together to form dithioalkylcarbonylhydrazide, where the hydrazide forms an hydrazone with the drug, or analog or derivative thereof.

35. The drug delivery conjugate of claim 1 wherein the bivalent linker comprises an heteroatom linker, a spacer linker, and a releasable linker taken
15 together to form 3-thiosuccinimid-1-ylalkylcarbonylhydrazide, where the hydrazide forms an hydrazone with the drug, or analog or derivative thereof.

36. The drug delivery conjugate of claim 1 wherein the bivalent linker comprises an heteroatom linker, a spacer linker, an heteroatom linker, a spacer linker, and a releasable linker taken together to form
20 3-thioalkylsulfonylalkyl(disubstituted silyl)oxy, where the disubstituted silyl is substituted with alkyl or optionally substituted aryl.

37. The drug delivery conjugate of claim 1 wherein the bivalent linker comprises a plurality of spacer linkers selected from the group consisting of the naturally occurring amino acids and stereoisomers thereof.

25 38. The drug delivery conjugate of claim 1 wherein the bivalent linker comprises a releasable linker, a spacer linker, and a releasable linker taken together to form 3-dithioalkyloxycarbonyl, where the carbonyl forms a carbonate with the drug, or analog or derivative thereof.

39. The drug delivery conjugate of claim 1 wherein the bivalent
30 linker comprises a releasable linker, a spacer linker, and a releasable linker taken together to form 3-dithioarylalkyloxycarbonyl, where the carbonyl forms a carbonate with the drug, or analog or derivative thereof, and the aryl is optionally substituted.

40. The drug delivery conjugate of claim 1 wherein the bivalent linker comprises an heteroatom linker, a spacer linker, a releasable linker, a spacer linker, and a releasable linker taken together to form 3-thiosuccinimid-1-ylalkyloxyalkyloxyalkylidene, where the alkylidene forms an hydrazone with the drug, or analog or derivative thereof, each alkyl is independently selected, and the oxyalkyloxy is optionally substituted with alkyl or optionally substituted aryl.

41. The drug delivery conjugate of claim 1 wherein the bivalent linker comprises a releasable linker, a spacer linker, and a releasable linker taken together to form 3-dithioalkyloxycarbonylhydrazide.

42. The drug delivery conjugate of claim 1 wherein the bivalent linker comprises a releasable linker, a spacer linker, and a releasable linker taken together to form 3-dithioalkylamino, where the amino forms a vinylogous amide with the drug, or analog or derivative thereof.

43. The drug delivery conjugate of claim 42 wherein the alkyl is ethyl.

44. The drug delivery conjugate of claim 1 wherein the bivalent linker comprises a releasable linker, a spacer linker, and a releasable linker taken together to form 3-dithioalkylaminocarbonyl, where the carbonyl forms a carbamate with the drug, or analog or derivative thereof.

45. The drug delivery conjugate of claim 44 wherein the alkyl is ethyl.

46. The drug delivery conjugate of claim 1 wherein the bivalent linker comprises a releasable linker, a spacer linker, and a releasable linker taken together to form 3-dithioarylalkyloxycarbonyl, where the carbonyl forms a carbamate or a carbamoylaziridine with the drug, or analog or derivative thereof.

47. A pharmaceutical composition comprising a drug delivery conjugate of claim 1, and a pharmaceutically acceptable carrier, diluent, or excipient therefor.

48. A method of eliminating a population of pathogenic cells in a host animal harboring the population of pathogenic cells wherein the members of the pathogenic cell population have an accessible binding site for a vitamin, or an analog or a derivative thereof, and wherein the binding site is uniquely expressed, overexpressed, or preferentially expressed by the pathogenic cells, said method

comprising the step of administering to said host a drug delivery conjugate of claim 1, or a pharmaceutical composition thereof.

49. A vitamin receptor binding drug delivery conjugate intermediate comprising:

- 5 (a) a vitamin receptor binding moiety;
(b) a bivalent linker, having a first end and a second end; and
(c) a coupling group;

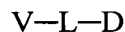
wherein the coupling group is a nucleophile, an electrophile, or a precursor thereof, capable of forming a covalent bond with a drug, or an analog or
10 derivative thereof;

the vitamin receptor binding moiety is covalently attached to the bivalent linker at the first end of the bivalent linker, and the coupling group is covalently attached to the bivalent linker at the second end of the bivalent linker; and

the bivalent linker comprises one or more components selected from
15 the group consisting of spacer linkers, releasable linkers, and heteroatom linkers, and combinations thereof; providing that the bivalent linker includes at least one releasable linker that is not a disulfide.

50. The intermediate of claim 49 wherein the vitamin receptor binding moiety is a vitamin, or a vitamin receptor binding analog or derivative
20 thereof.

51. A vitamin receptor binding drug delivery conjugate having the formula:

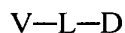


wherein L is selected from the group consisting of $(I_s)_a$, $(I_H)_b$, and $(I_r)_c$,
25 and combinations thereof; where (I_r) is a releasable linker, (I_s) is a spacer linker, and (I_H) is an heteroatom linker;

V is a vitamin receptor binding moiety, and D is a drug, or an analog or a derivative thereof; and

a, b, and c are each independently 0, 1, 2, 3, or 4;
30 providing that L includes at least one (I_r) that is not a disulfide.

52. A vitamin receptor binding drug delivery conjugate having the formula:



wherein L is selected from the group consisting of $(I_s)_a$ and $(I_H)_b$, and combinations thereof; where (I_s) is a spacer linker and (I_H) is an heteroatom linker; and a and b are each independently 0, 1, 2, 3, or 4; and

V is a vitamin receptor binding moiety, and D is a drug, or an analog or a derivative thereof.

53. The drug delivery conjugate of claim 52 wherein the drug is a hapten.

54. The drug delivery conjugate of claim 53 wherein the hapten is selected from the group consisting of fluorescein and dinitrophenyl.

55. A pharmaceutical composition comprising a drug delivery conjugate of claim 1, and a pharmaceutically acceptable carrier, diluent, or excipient therefor.

56. A method of eliminating a population of pathogenic cells in a host animal harboring the population of pathogenic cells wherein the members of the pathogenic cell population have an accessible binding site for a vitamin, or an analog or a derivative thereof, and wherein the binding site is uniquely expressed, overexpressed, or preferentially expressed by the pathogenic cells, said method comprising the step of administering to said host a drug delivery conjugate of claim 1, or a pharmaceutical composition thereof.

57. A vitamin receptor binding drug delivery conjugate intermediate comprising:

- (a) a bivalent linker, having a first end and a second end;
- (b) a drug, or an analog or a derivative thereof; and
- (c) a coupling group;

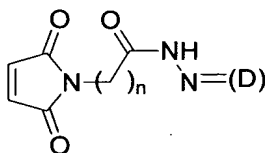
wherein the bivalent linker comprises one or more components selected from the group consisting of spacer linkers, releasable linkers, and heteroatom linkers, and combinations thereof; providing that the bivalent linker includes at least one releasable linker that is not a disulfide;

the coupling group is a nucleophile, an electrophile, or a precursor thereof, capable of forming a covalent bond with a vitamin receptor binding moiety; and

the coupling group is covalently attached to the bivalent linker at the first end of the bivalent linker, and the drug, or analog or derivative thereof is covalently attached to the bivalent linker at the second end of the bivalent linker.

58. The intermediate of claim 57 wherein the vitamin receptor binding moiety is a vitamin, or a vitamin receptor binding analog or derivative thereof; the coupling group is a Michael acceptor; and the bivalent linker includes a releasable linker having a formula selected from the group consisting of $-C(O)NHN=$, $-NHC(O)NHN=$, and $-CH_2C(O)NHN=$.

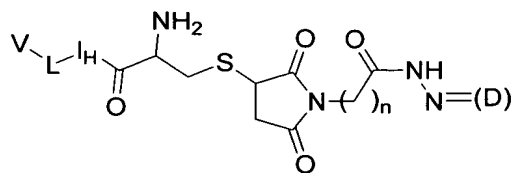
59. The intermediate of claim 57 wherein the bivalent linker comprises a first releasable linker, and a first spacer linker; and the first releasable linker, the first spacer linker, and the coupling group are taken together to form a compound having the formula:



- where D is the drug, or an analog or a derivative thereof, and n is an integer selected from the group consisting of 1, 2, 3, and 4.

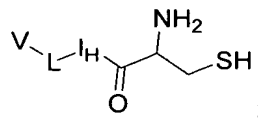
60. The intermediate of claim 59 wherein the vitamin receptor binding moiety includes an alkylthiol nucleophile.

61. A process for preparing a compound having the formula:



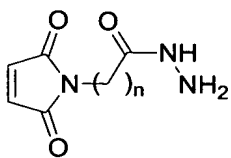
- where V is a vitamin receptor binding moiety; L is selected from the group consisting of $(l_r)_c$, $(l_s)_a$, and $(l_H)_b$, and combinations thereof, where (l_r) is a releasable linker, (l_s) is a spacer linker, (l_H) is an heteroatom linker, and a, b, and c are integers selected from the group consisting of 0, 1, 2, 3, and 4; and D is a drug, or an analog or a derivative thereof; comprising:

- (a) reacting a compound having the formula:



with a compound having the formula:

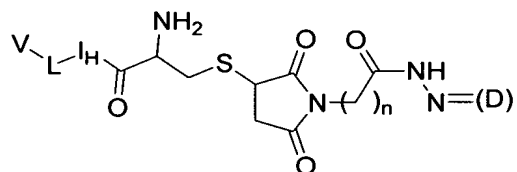
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; and

(b) forming a hydrazone derivative of the drug, or the analog or derivative thereof.

62. A process for preparing a compound having the formula:

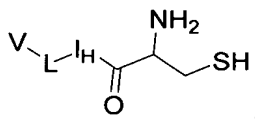


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where V is a vitamin receptor binding moiety; L is selected from the group consisting of $(I_r)_c$, $(I_s)_a$, and $(I_H)_b$, and combinations thereof, where (I_r) is a releasable linker, (I_s) is a spacer linker, (I_H) is an heteroatom linker, and a, b, and c are integers selected from the group consisting of 0, 1, 2, 3, and 4; and D is a drug, or an analog or a derivative thereof; comprising:

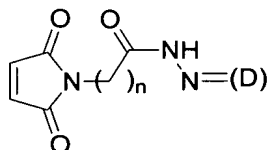
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reacting a compound having the formula:



;

with a compound having the formula:



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63. The process of claim 62 wherein the drug or the analog or derivative thereof is selected from the group consisting of daunomycins, daunomycinones, daunorubicins, aclamycins, taxols, chromomycins, and aurilic acids.